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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
05/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/528,073	VALKNA ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-23 and 26-30* is/are pending in the application.

4a) Of the above claim(s) *27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/17/05 and 8/5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 19-23 and 26-30 are all the pending claims for this application.

2. The preliminary amendments to the specification of 1/19/04 and 11/7/05 have been considered and entered.

Election/Restrictions

3. Applicant's election with traverse of Group I (Claims 19-23 and 26) as to Group III in the reply filed on 3/12/08 is acknowledged.

a) The traversal is on the ground(s) that Groups I and III should be rejoined since they are both related by the same technical feature. Applicants allege that Zhao's methods involve chemical attachment of MTS sequences to proteins by NaIO4 whereas the membrane penetrating sequence of the invention is part of the fusion protein, and further that one could not combine the disclosures of Toftgrad, WO 01/12655 with Zhao to break unity of invention.

This is not found persuasive because the means by which the MTS peptide (cell membrane penetrating peptide) is conjugated to the antibody in Zhao is irrelevant to the instant claimed product invention. No mention much less a requirement is made for how the fusion protein is created or what the physical relationship is between the elements of the fusion protein. Instant claim 19 of the first claimed product is drawn to any scfv -part of an antibody and any cell-penetrating transport peptide and each of these elements are "at least" what comprise a fusion protein. The language in Claim 19 including "comprising" and "at least (a)…and (b)" are in no way suggestive that the scFv-part and

the cell penetrating transport peptide are themselves required to expressed as a single protein from a common transcript. Still further and at least according to Example 3 of the specification, the "fusion protein" of the invention was prepared by conjugating a maleimide-derivatized peptide to the monoclonal antibody for GLi1 and GLi3.

The motivation to combine Zhao with Toftgard, Rothbard and Lindgren is discussed on p. 3 of the Office Action of 2/12/08 and incorporated herein.

The requirement is still deemed proper and is therefore made FINAL.

b) The traversal to rejoin Groups I-III is on the grounds that search and examination of all the groups could be made without serious burden.

Applicants are reminded that an Examiner is not required to establish a search burden in finding lack of unity or where a lack of unity restriction is required. Chapter 1800 of the MPEP does not speak to this issue.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 27-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/12/08.

5. Claims 19-23 and 26 are all the pending claims under examination.

Information Disclosure Statement

6. The information disclosure statement filed 3/17/05 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each

non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. However, the U.S. patent reference AA has been considered. The copy of the examiner's initialed 1449 form is attached. Applicants are invited to furnish copies of the references cited therein.

7. The references filed in the IDS of 8/5/05 have been considered. The copy of the examiner's initialed 1449 form is attached.

Application Disclosure Statement

8. The Application Data Sheet filed 3/17/05 is not in compliance under MPEP 601.05 or 37 CFR 1.76. For the requirements of an ADS, please refer to 37 CFR 1.76 (b). A supplemental ADS to correct the information may be filed pursuant to 37 CFR 1.76(c).

Specification

9. The specification is objected to for the following reasons:

a) the specification discloses a peptide sequence of $\geq$ 4 amino acids in length and fails to provide a sequence identifier pursuant to 37 CFR 1.821-1.825: see p. 9, line 15: (Gly4Ser)3;

b) the legend to Figure 2 is objected to because it has the same description for panels 2A and 2C and the same description for panels 2B and 2D. It is not clear what the difference is between panels 2A and 2C and panels 2B and 2D;

c) the legend to Figure 3 is objected to because it is unclear what is meant by recombinant protein. Is the fusion protein the same as described in Example 7 of the specification?

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 22 is indefinite for the recitation "wherein the scFv-part is derived from the human genome" because it is unclear what the phrase "derived from" encompasses. The primary deficiency in the use of the term "derived from" is the absence of an ascertainable meaning for the phrase. The scFv is an antibody fragment that is not full length, and it is not clear if a derivative can encompass amino acid substitutions, insertions, deletions, or even antibody mimetics. Are applicants referring to an antibody from which the scFv is derived, or do they mean that a naturally occurring gene exists in a human genome encoding a wild-type scFv? Do Applicants mean a transgenic human genome containing a gene encoding a scFv? A scFv is generally thought of as a recombinant form of an antibody, and where the parent antibody from which the VH and VL domains is encoded by the human genome. In the absence of a single defined art recognized meaning for the phrase "derivative" and lacking a definition of the phrase in the specification, one of skill in the art could not determine the metes and bounds of the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

11. Claims 23 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a diagnostic use (e.g., medical or pharmaceutical) for in vitro cell uptake of a "fusion protein" comprising a cell-penetrating transport peptide (CPP)-anti-GLi-1 or anti-GLi-3 polyclonal or monoclonal antibody, or the GLI-1 scfv or the GLI-3 scFv fused to a CPP (e.g., VL-CPP -linker-VH), does not reasonably provide enablement for a therapeutic use of the fusion protein in any subject in vivo for any disease including cancer much less where the subject is a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the invention/ Skill in the Art

The claims are interpreted as follows: Claim 23 is drawn to any fusion protein comprising at least any scFv-part of any antibody and any cell penetrating transport peptide (CPP) of Claim 19 with the fusion protein having any medical use. Claim 26 is

drawn to a pharmaceutical composition comprising at least one fusion protein of Claim 19 in association with at least one pharmaceutically acceptable carrier or additive.

The relative skill in the art required to practice the invention is a clinical diagnostician with a background in antibody-based methods.

Disclosure in the Specification

The specification teaches in general that cancer-specific antibodies to cancer-specific intracellular signals can be used for treatment of diseases by modulating the uptake of the antibodies into disease-affected cells in order to inactivate the intracellular targets (p. 2, lines 17). The specification teaches that "delivery of the scFv intrabodies remains a problematic issue for their potential therapeutic applications (p. 3, lines13-14). To solve this problem, the specification teaches peptide-mediated membrane penetration to deliver antibodies or scFvs to intracellular target proteins (p. 3, lines 17-20). The specification describes the fusion proteins for use in the treatment of a disease or health disorder in "humans or animals" (p. 5, lines 1-2). The specification describes cell penetrating peptides (CPPs) such as transportan for transporting antibodies into cells (p. 4, lines 3-4).

Working examples in the specification are the following:

Example 3 (working): describes conjugating CPP (transportan 10) to polyclonal antibodies for GLI1 and GLI3. The anti-GLI1-CPP conjugate is described as being shown in Figure 2 to be taken up after 3 and 14 hour incubations by Cos-1 cells compared to unconjugated GLI-1.

Example 7 (working): describes making a fusion protein from the cloned VH and VL domains of the anti-GLI-1 or GLI-3 antibody and being linked with a linker where the CPP (9Arg or Transportan or Transportan 10) is interposed between the VL and linker portion of the molecule (e.g., VL-TP-linker-VH). The specification teaches that the antibodies bind to the GL1 protein and also entered eukaryotic cells in culture. ***If*** the data in Figure 3 correspond to this example, then it appears the anti-GLI1 scfv-TP embodiment is taken up into human 293 cells in vitro.

The specification is insufficient and therefore non-enabling in its disclosure for using any fusion protein comprising any scfv fused to any CPP in any medical use or any pharmaceutical application, because of the limited number of working embodiments which are shown to a) have uptake or increased uptake by cells by virtue of the CPP, and more importantly, b) that the internalized fusion protein retains specific antigen binding, yet would still have an inactivating effect on the target antigen through the scfv. The specification has not provided a single working example of any fusion protein demonstrating all of these properties, therefore, because the ordinary artisan could not predict which combination of scfv and CPP could be used together to impart to a fusion protein all of the preceding properties, the ordinary artisan would be required to perform undue trial and error experimentation in order to practice the invention as claimed. The specification is even less enabling for using the fusion protein in vivo to treat any disorder in any subject much less where the subject is a human. The specification is not enabling for using the fusion protein to treat any cancer in vitro or in vivo. The specification provides an enabling disclosure for using the fusion protein to identify

intracellular target antigens, which might otherwise be difficult to detect with a scfv absent the CPP moiety, and which could have applications for in vitro diagnostics. Otherwise, one of skill in the art could not deduce from the specification which of the myriad combinations of scfv and CPP encompassed by the claims and the myriad medical uses especially where the intended medical use was treating any cancer, would be effective in humans or animals.

Prior Art Status: Translation of Therapeutics from In vitro to In vivo is Unpredictable

The claims encompass using the fusion protein in any medical application or impliedly in unlimited pharmaceutical applications. The specification explicitly contemplates using the fusion protein for cancer therapy in animals and humans.

A tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and drug access to the tumor cells are not evenly distributed and this is an important source of heterogeneity in tumor response to drugs. Therefore, prediction of drug effects in any animal model or even a human based solely on a single in vitro experiment as in the present case is not reliable and further evaluation in animal disease model systems is essential.

Further, inasmuch as in vitro drug testing *may be* a platform technology in a determination of enablement, the complexity and difficulty of antibody delivery for cancer treatment is underscored by Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-

clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4)

telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar.

Cespdes et al. (Clin. Transl. Oncol. 8(5):318-329 (2006)) review the some of the examples of art-recognized animal disease model correlates for the corresponding human disease in Tables 1-3. Cespedes emphasizes the challenges in using animal models as predictive correlates for human responsiveness to therapeutics and sets forth on pp. 318-319 a list of criteria that would represent the ideal in vivo model for studying cancer therapeutics. As regards the use of xenograft modeling, Cespedes teaches:

> "One limitation of the xenograft models is precisely their use of an immunocompromised host, which eliminates the possibility of studying the role of the immune system in tumor progression. Some authors also think that cancer and host cells being from different species may limit the occurrence of critical tumor-stroma interactions, leading to an inefficient signaling. The organ of implantation could also become a limitation to the system. Thus, as it has already been described, subcutaneous xenografts infrequently metastasize and are unable to predict response to drugs" (p. 325, Col. 1, ¶2).

At least for the HIV TAT peptide conjugate to the scfv for ED-B domain of fibronectin (Niesner et al., Bioconjug. Chem. 13(4): 729-736 (Jul-Aug 2002); Abstract), Niesner teaches that tumor targeting in vivo was severely reduced compared to the

unconjugated antibody. Niesner teaches that the poor biodistribution of TAT-antibody conjugates casts doubt on the applicability of the method for delivery in vivo.

One skilled in the art based on the prior art teachings and the insufficiency of enabling data in the specification, would reasonably conclude that evidence obtained from a limited number of in vitro cell assays would not even necessarily correlate with results expected in any animal model much less a human subject.

Unpredictability/ Undue Experimentation

Given the unpredictability of translational experimentation for drugs and antibodies from in vitro cell-based assays to animal models much less to human trials and the insufficient experimental data provided in the specification, the ordinary artisan would be forced into undue experimentation to practice using the fusion protein for any medical condition or for any pharmaceutical application especially where an intended therapeutic effect was to be observed in vivo.

Priority

12. The copy of the foreign language priority document, Estonia P200200531 (filed 9/17/02), was received by the Office. However, a certified translation has not been provided by Applicants. Therefore, the instant claimed invention obtains benefit of the international filing date, 9/16/03, for PCT/EE03/00005.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 19, 23 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (J. Method. Immunol. 254:137-145 (2001); cited in the PTO 892 form of 2/12/08) as evidenced by Pavlinkova et al. (J. Immunol. Methods 201:77-88 (1997)).

Claim 19 is interpreted as being drawn to any scfv and any cell-penetrating transport peptide where each of these elements is “at least” what comprises a fusion protein. The structure of the protein and the elements linking the two moieties are interpreted as being unlimited given the comprising language. Claim 23 is interpreted as being drawn to using the fusion protein of Claim 19 to visualize an intracellular antigen for diagnosing, for example. Claim 26 is interpreted as a pharmaceutical composition comprising the fusion protein of Claim 19.

Because of the indefiniteness of Claim 22 as discussed above, the claim is not included under the rejection.

Zhao discloses cross-linking an MTS peptide (membrane translocating sequence) derived from the signal region of Kaposi fibroblast growth factor to the 5D10 monoclonal antibody in order to render the antibody cell- permeable for live cells in vitro (e.g., Figure 4), where the complex is diluted in PBS and administered to cells in vitro. This is interpreted as reading on a pharmaceutical composition. The complex allows visualization of intracellular antigens for diagnostic purposes. Zhao teaches that the approach of linking an MTS can be performed on any antibody (p. 144, Col. 2, last line). Zhao teaches thru incorporation by reference to Pavlinkova that small peptides can be introduced into scfv antibodies, providing as indirect support, the manipulation of scfvs for modification to include MTS peptides and to enhance Fv uptake into cells.

14. Claim 19, 21, 23 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08).

The interpretation of Claims 19, 23 and 26 is discussed above under section 13. Claim 21 is interpreted as being drawn to the fusion protein of Claim 19 where the cell transport peptide is Arg 9.

Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that "the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells" (p. 25, lines 10-21). Rothbard explicitly teaches fusion polypeptides comprising the polypeptide of interest and the transport peptide (p. 15, lines 15-20; p. 25, lines 29-31). Rothbard teaches that targets can be visualized with the fusion proteins (Example 4) and using the fusion proteins in pharmaceutical compositions (p. 7, lines 9-12).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 19, 20, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao et al. (J. Method. Immunol. 254:137-145 (2001); cited in the PTO 892 form of 2/12/08) as evidenced by Pavlinkova et al. (J. Immunol. Methods 201:77-88 (1997)) in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08).

Claim 19 is interpreted as being drawn to any scfv and any cell-penetrating transport peptide where each of these elements is "at least" what comprises a fusion protein. The structure of the protein and the elements linking the two moieties are interpreted as being unlimited given the comprising language. Claim 20 is interpreted as being drawn to an anti- GLI protein scfv, where the protein is GLI-1 or GLI-3, and any cell-penetrating transport peptide where each of these elements is "at least" what comprises a fusion protein. The structure of the fusion protein and the elements linking the two moieties are interpreted as being unlimited given the comprising language. Claim 23 is interpreted as being drawn to using the fusion protein of Claim 19 to visualize an intracellular antigen for diagnosing, for example. Claim 26 is interpreted as a pharmaceutical composition comprising the fusion protein of Claim 19.

Because of the indefiniteness of Claim 22 as discussed above, the claim is not included under the rejection.

The claimed fusion proteins were prime facie obvious at the time of the invention over Zhao as evidenced by Pavlinkova in view of Toftgard.

Zhao discloses cross-linking an MTS peptide (membrane translocating sequence) derived from the signal region of Kaposi fibroblast growth factor to the 5D10 monoclonal antibody in order to render the antibody cell- permeable for live cells in vitro (e.g., Figure 4), where the complex is diluted in PBS and administered to cells in vitro. This is interpreted as reading on a pharmaceutical composition. The complex allows visualization of intracellular antigens for diagnostic purposes. Zhao teaches that the approach of linking an MST can be performed on any antibody (p. 144, Col. 2, last line). Zhao teaches thru incorporation by reference to Pavlinkova that small peptides can be introduced into scfv antibodies, providing as indirect support, the modification of scfvs to include cell membrane transport peptides. Zhao appreciates introducing cell membrane penetrating peptides into unlimited antibodies including scfvs as further evidenced by Pavlinkova, but does not teach scfvs for the family of GLI proteins for GLI-1 or GLI-3, whereas does Toftgard.

Toftgard discloses the GLI-1 protein (see entire document) and the GLI-3 protein (pp. 3, 24 and 36) and making antibodies against these intracellular antigens (p. 12, lines 1-14). Included amongst the antibodies are single chain antibodies and pharmaceutical compositions comprising the antibodies and carriers (p. 3, line 25; p. 12, lines 16-20; p. 13, lines 10-15). Toftgard teaches the technology for making protein fusion constructs in general (p. 28, lines 15-16).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide based on the combined disclosures of Zhao as evidenced by Pavlinkova in view of Toftgard. All of the references appreciate and expressly teach the utility of scfv antibodies. Thus in order to visualize an intracellular antigen such as GLI-1 and GLI-3 as taught by Toftgard or the intracellular antigen of Zhao, the ordinary artisan would have been motivated to have modified an antibody into a scfv not only to decrease the size, but to include a cell membrane permeating peptide such as taught by Zhao in order to facilitate or increase cellular uptake of the antibody into a cell in vitro. In order to detect or visualize an intracellular antigen that was otherwise not accessible to the antibody without permeabilizing the cell itself, one would have been motivated to have engineered a fusion protein where Toftgard and Pavlinkova provided the methods for making fusion constructs and more especially Pavlinkova's teaching of scfvs, to include a cell penetrating peptide based on Zhao. The ordinary artisan would have been motivated at the time of the invention to engineer the cell penetrating peptide to the scfv so that whole cells could be examined in vitro without affecting cell structure or viability (see Zhao at p. 138, Col. 1, ¶1). The ordinary artisan would have been motivated in producing the fusion protein for a diagnostic visualization of intracellular antigen expression in screening cells in vitro and where the fusion protein was formulated into a pharmaceutical composition compatible for administration to living cell in vitro. The ordinary artisan would have been reasonably assured of success in having produced or used the fusion protein for limited applications in vitro because the

methods and materials for scfvs and cell penetrating peptides were already available based on the combined disclosures of the cited references, the construction of fusion proteins was already well known based on the combined disclosures of Toftgard and Pavlinkova, and producing a scfv by introduction of a peptide in order to facilitate cellular uptake of the antibody had already been accomplished by Zhao as evidenced by Pavlinkova. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Zhao as evidenced by Pavlinkova and Toftgard.

16. Claims 19-21, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao et al. (J. Method. Immunol. 254:137-145 (2001); cited in the PTO 892 form of 2/12/08) as evidenced by Pavlinkova et al. (J. Immunol. Methods 201:77-88 (1997)) in view of in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08) as applied to claims 19, 20, 23 and 26 above, and further in view of Rothbard (WO/ 98/52614; cited in the PTO 892 form of 2/12/08) and Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08).

The interpretation of Claims 19, 20, 23 and 26 is discussed above under section 15. All of the claims encompass the fusion protein comprising a cell penetrating transport peptide. Claim 21 is further drawn to the peptide of Claim 19 comprising at least a part of Transportan, Transportan 10 or Arg 9.

Because of the indefiniteness of Claim 22 as discussed above, the claim is not included under the rejection.

The claimed fusion proteins were prime facie obvious at the time of the invention over Zhao as evidenced by Pavlinkova in view of Toftgard and further in view of Rothbard and Lindgren.

The interpretation of Zhao as evidenced by Pavlinkova in view of Toftgard is discussed above under section 14. Zhao appreciates intracellular targeting of antibody scfv's using membrane penetrating peptides conjugated to scfv, and Toftgard and Pavlinkova appreciate scfvs and making fusion protein constructs, but do no expressly teach the peptides for transportan, transportan 10 or Arg9, whereas do Rothbard and Lindgren.

Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that "the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells" (p. 25, lines 10-21).

Lindgren teaches cell penetrating peptides for transportan (Table 1, Table 2, p. 99, Col. 1), and the use of this and other peptides for cellular delivery of drugs or research tools (p. 102, Col. 2).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide based on the combined disclosures of Zhao as evidenced by Pavlinkova in view of Toftgard and further in view of Rothbard and

Lindgren. Zhao as evidenced by Pavlinkova in view of Toftgard provide the motivation to produce fusion proteins comprising a sfv and a cell membrane penetrating peptide to facilitate transport of the scfv into a viable cell in vitro for whole cell visualization of the targeted antigen. One skilled in the art would have found more than sufficient motivation to substitute different cell membrane penetrating peptides in the fusion protein comprising the scfv based on Zhao and Rothbard because each explicitly teach the advantages of small antibody forms like scfv and transport peptides which could be used to facilitate cell entry of the scfv. Rothbard and Lindgren teach different structural classes of transport peptides encompassing transportan and Arg 9 and provide the explicit motivation to use the peptides to convey molecules across cell membranes that would otherwise be impermeable. The ordinary artisan would have been reasonably assured of success in having produced the fusion proteins and used them to visualize a target antigen in vitro in whole, living cells because as between all of the references all of the methods and reagents were already available and had been shown to work in related molecules for similar purposes. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Zhao as evidenced by Pavlinkova and Toftgard in view of Rothbard and Lindgren.

17. Claims 19, 21, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08) in view of Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08).

Claim 19 is interpreted as being drawn to any scfv and any cell-penetrating transport peptide where each of these elements is "at least" what comprises a fusion protein. The structure of the protein and the elements linking the two moieties are interpreted as being unlimited given the comprising language. Claim 21 is interpreted as being drawn to the fusion protein of Claim 19 where the cell transport peptide is transportant or Arg 9. Claim 23 is interpreted as being drawn to using the fusion protein of Claim 19 to visualize an intracellular antigen for diagnosing, for example. Claim 26 is interpreted as a pharmaceutical composition comprising the fusion protein of Claim 19.

Because of the indefiniteness of Claim 22 as discussed above, the claim is not included under the rejection.

The claimed fusion proteins were prime facie obvious at the time of the invention over Rothbard in view Lindgren.

Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that "the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells" (p. 25, lines 10-21). Rothbard explicitly teaches fusion polypeptides comprising the polypeptide of interest and the transport peptide (p. 15, lines 15-20; p. 25, lines 29-31). Rothbard teaches that targets can be visualized with the fusion proteins (Example 4) and using the fusion proteins in pharmaceutical compositions (p. 7, lines 9-12). Rothbard explicitly teaches

transport peptides fused to scfv but does not disclose transportan as a species whereas does Lindgren.

Lindgren teaches cell penetrating peptides for transportan (Table 1, Table 2, p. 99, Col. 1), and the use of this and other peptides for cellular delivery of drugs or research tools (p. 102, Col. 2).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide at the time of the invention based on the combined disclosures of Rothbard in view Lindgren. One skilled in the art would have been motivated to produce fusion proteins comprising a sfv and a cell membrane penetrating peptide to facilitate transport of the scfv into a viable cell in vitro for whole cell visualization of the targeted antigen based on the disclosure or Rothbard alone. One skilled in the art would have found more than sufficient motivation to substitute different cell membrane penetrating peptides in the fusion protein comprising the scfv based on Rothbard because Rothbard explicitly teaches the advantages of small antibody forms like scfv and transport peptides such as Arg 9 peptides which could be used to facilitate cell entry of the scfv, and Lindgren teaches different structural classes of transport peptides encompassing transportan to deliver agents into cells that would otherwise be impermeable. The ordinary artisan would have been reasonably assured of success in having produced the fusion proteins and used them to visualize a target antigen in vitro in whole, living cells because as between all of the references, all of the methods and reagents were already available and had been shown to work in related

molecules for similar purposes. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Rothbard and Lindgren.

18. Claims 19-21, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08) in view of Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08) as applied to claims 19, 21, 23 and 26 above, and further in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08).

The interpretation of Claims 19, 21, 23 and 26 is discussed above under section 17. Claim 20 is interpreted as being drawn to a fusion protein comprising an anti- GLI protein scfv, where the protein is GLI-1 or GLI-3, and any cell-penetrating transport peptide where each of these elements is “at least” what comprises the fusion protein.

Because of the indefiniteness of Claim 22 as discussed above, the claim is not included under the rejection.

The claimed fusion proteins were prime facie obvious at the time of the invention over Rothbard in view Lindgren and Toftgard.

The interpretation of Rothbard in view Lindgren is discussed above under section 17. Rothbard appreciates scfv directed against many different target antigens and using the scfvs in the form of a fusion protein with a transport peptide to mediate or facilitate uptake but does not disclose the scfv recognizing GLI proteins such as GLI-1 and GLI-3, whereas does Toftgard.

Toftgard discloses the GLI-1 protein (see entire document) and the GLI-3 protein (pp. 3, 24 and 36) and making antibodies against these intracellular antigens (p. 12, lines 1-14). Included amongst the antibodies are single chain antibodies, and pharmaceutical compositions comprising the antibodies and carriers (p. 3, line 25; p. 12, lines 16-20; p. 13, lines 10-15). Toftgard teaches the technology for making protein fusion constructs in general (p. 28, lines 15-16).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide at the time of the invention based on the combined disclosures of Rothbard and Lindgren in view of Toftgard. Rothbard and Toftgard appreciate and expressly teach the utility of scfv antibodies. Thus in order to visualize an intracellular antigen such as GLI-1 and GLI-3 as taught by Toftgard or an intracellular antigen of Rothbard, the ordinary artisan would have been motivated to have modified an antibody into a scfv not only to decrease the size, but to include a cell membrane permeating peptide such as taught by Rothbard and Lindgren in order to facilitate or increase cellular uptake of the antibody into a cell in vitro. In order to detect or visualize an intracellular antigen that was otherwise not accessible to the antibody without permeabilizing the cell itself, one would have been motivated to have engineered a fusion protein where Rothbard abd Toftgard provided the methods for making fusion constructs and more especially Rothbard's 's teaching of scfvs, to include a cell penetrating peptide including Arg 9 and the peptides of Lindgren. The ordinary artisan would have been motivated at the time of the invention to engineer the cell

penetrating peptide to the scfv so that whole cells could be examined in vitro without affecting cell structure or viability. The ordinary artisan would have been motivated in producing the fusion protein for a diagnostic visualization of intracellular antigen expression in screening cells in vitro and where the fusion protein was formulated into a pharmaceutical composition compatible for administration to living cell in vitro. The ordinary artisan would have been reasonably assured of success in having produced or used the fusion protein for limited applications in vitro because the methods and materials for scfvs and cell penetrating peptides were already available based on the combined disclosures of the cited references, the construction of fusion proteins was already well known based on the combined disclosures of Rothbard and Toftgard, and producing a scfv by introduction of a peptide in order to facilitate cellular uptake of the antibody had already been accomplished by Rothbard. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Rothbard, Lindgren and Toftgard.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
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